

Anticoagulant Therapy in Heart Disease

A Summary of the Literature

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SUMMARY

Considerable experience by many independent workers with the use of anticoagulants in the treatment of certain types of heart disease has shown that such therapy reduces significantly the incidence of thromboembolic complications and, largely through this effect, the morbidity and mortality rate from heart disease of these types.

This is certainly established in acute coronary occlusion with myocardial infarction and in those instances of rheumatic heart disease with auricular fibrillation in which repeated embolic phenomena have occurred. The case for the administration of the anticoagulants in congestive heart failure is less secure, although there is no doubt that the number of thromboembolic complications is reduced by use of them.

The administration of the anticoagulants requires considerably more exacting attention than does the administration of the majority of therapeutic agents in use commonly today. Hence, it is suggested that the use of anticoagulants in heart disease be restricted to those instances in which the indications are clear and facilities are compatible with the efficient and safe use of the drug, whether Dicumarol or heparin.

THE use of the anticoagulants in the prevention and treatment of thromboembolic phenomena clinically is well established.^{1, 10, 11, 13, 15, 18, 38} Hines and Barker¹⁰ assert that "anticoagulant therapy is the best method for preventing thrombosis and embolism which is available at present." They list the following situations in which the use of anticoagulants may be advisable in chronic cardiovascular diseases:

A. Treatment of single episodes of thrombosis, or embolism.

1. Acute arterial occlusion (including coronary artery occlusion).
2. Acute thrombophlebitis, or phlebothrombosis.
3. Pulmonary embolism, or infarction.

B. Prevention of recurring episodes of thrombosis.

C. Long-term treatment of the disease (only in certain situations).

This summary is confined arbitrarily to the use of the anticoagulants in heart disease and omits reference to use of them in diseases involving primarily the vascular system outside the heart.

ANTICOAGULANT THERAPY IN ACUTE CORONARY OCCLUSION WITH MYOCARDIAL INFARCTION

The use of anticoagulants in the prevention and treatment of coronary thrombosis with myocardial infarction was suggested by Best and co-workers in a report on a series of animal experiments on intravascular clotting. These investigators produced intravascular clots in systemic veins by both mechanical and chemical methods. They demonstrated that the incidence of such artificially produced intravascular clots could be reduced dramatically by the use of heparin.

In 1938, Solandt and Best²⁹ produced coronary thrombosis regularly in experimental animals by injecting a solution of sodium ricinoleate into an isolated coronary artery. A thrombus formed in almost every instance when no heparin was used. When the animals were heparinized prior to the injection of ricinoleate, thrombus formation was a rare occurrence.

Solandt, Nassim and Best³⁰ produced large mural thrombi in the left ventricles of experimental animals by ligating the anterior descending branch of the left coronary artery and injecting sodium ricinoleate into the subendocardial myocardium. A large mural thrombus formed promptly and consistently when the animals were not heparinized. When heparin was given well before the experiment, no mural thrombi formed.

Heparin or Dicumarol* was used clinically in individual cases, or in small series of cases of coronary occlusion with myocardial infarction during 1941 and 1942. The first American report concerned exclusively with the use of Dicumarol in acute coronary occlusion appeared in December 1945 when Wright³⁴ described experience with 76 patients. Between the time of that report and 1949, approximately two dozen series of cases were reported in the American literature. As reflected in the literature, the greatest experience with this means of therapy was obtained by Peters and Brambel^{26, 27} in Baltimore, by Nichol^{19, 20, 23} in Miami, by Parker and Barker^{24, 25} at the Mayo Clinic, and by Wright and his associates^{35, 36, 37, 39, 40} in New York City.

*Dicumarol is the registered collective trademark of the Wisconsin Alumni Research Foundation which controls the use thereof.

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The results obtained, while consistently favorable, were in no instance based upon a sufficient number of cases, nor upon sufficiently well controlled case material to warrant statistical analysis. They did, however, justify the more extensive study carried out by the American Heart Association's committee for the evaluation of the anticoagulants in the treatment of coronary occlusion with myocardial infarction.

THE AMERICAN HEART ASSOCIATION STUDY

Members of this committee, associated with the 16 hospitals in which the patients included in the study were treated, observed over 1,000 cases of coronary occlusion with myocardial infarction. Somewhat fewer than half of the patients were treated by conventional methods alone. The others received anticoagulants as well. A record of each case was forwarded on master forms to the central office at the New York Hospital where it was studied and the data tabulated for intensive statistical analysis.

A definitive report on the 1,031 case reports accepted for analysis is being prepared and will be published as a monograph. The data and conclusions quoted here are those contained in the preliminary report of the committee based upon a gross analysis of the first 800 cases collected.^{39, 40} Comparable figures based upon the total 1,031 cases are known to be not significantly different and to support the same conclusions.

Twenty-four per cent of the control group and 15 per cent of the anticoagulant-treated patients died during the six-week period of observation. Deaths following one or more thromboembolic complications occurred in roughly 10 per cent of the control group and in 3 per cent of the treated patients. Deaths not preceded by a clinically recognized complication occurred in approximately 14 per cent of the control group and in 12 per cent of the treated group. Anticoagulants reduced the death rate largely by reducing the number of deaths due directly or indirectly to thromboembolism.

The death rates by week of illness were highest during the first two weeks, but were still considerable through the fourth week. For each period the death rate for the control patients was significantly higher than that for the treated group. To give maximum protection, anticoagulants should be continued for at least four weeks after the last thromboembolic episode.

The greatest reduction of mortality was in patients 60 years of age or older. While the crude death rates for patients under 59 years of age in both the treated and control groups did not show a significant difference, the incidence of thromboembolic complications was high in the younger age groups and the incidence of thromboembolic complications was much lower in the treated than in the control group.

Twenty-five per cent of the control patients and 11 per cent of the treated patients had at least one

thromboembolic complication. However, in the treated group, the first complication developed in 3.5 per cent of patients before they had received any anticoagulant and 1.5 per cent during the first three days of anticoagulant therapy, before Dicumarol is ordinarily fully effective. Thromboembolic complications developed in only 6 per cent of the patients during the time they were under the full effect of anticoagulant therapy.

The number of thromboembolic complications diagnosed clinically per 100 cases was 36 in the control group and 14 in the treated group. Only 6.5 thromboembolic complications per 100 treated cases occurred in patients who were under the full therapeutic effect of anticoagulant therapy. This figure includes some complications in patients who were not under adequate anticoagulant therapy at the time the complication occurred.

The highest incidence of thromboembolic complications among the control patients occurred in the age group between 50 and 59 years, in distinct contrast to the death rate by age groups. Apparently, younger patients have thromboembolic complications commonly but are able to survive them. Older patients are more liable to succumb to the first thromboembolic attack. This indicates the importance of preventing thromboembolic phenomena in all age groups. Within the treated group, when distinction is made between those patients who were and those who were not receiving anticoagulants at the time of the complication, the effects of anticoagulant therapy are further emphasized.

When the rates of thromboembolic complications by week of illness are considered, the advantage of using anticoagulants is clearly demonstrated through the first four weeks of the illness. Since it is impossible to predict during the first week whether thromboembolic complications will develop during subsequent weeks, it is important to give anticoagulant therapy to all patients with coronary occlusion and myocardial infarction unless specific contraindications exist.

Patients receiving Dicumarol had a distinctly better chance of escaping thromboembolic complications of every type and at every site than did those who received conventional therapy alone.

The incidence of severe hemorrhage resulting from anticoagulant therapy was extremely low. Of the 30 hemorrhages observed clinically, 15 were mild, 14 were moderate, and only one was severe.

EXPERIMENTAL OBSERVATIONS

Blumgart and his co-workers^{4, 5} produced experimental myocardial infarction in dogs by ligating the anterior descending coronary artery. Dicumarol was administered to some animals, and heparin and Dicumarol to others, immediately following the operation, in order to determine if adverse myocardial changes might result from anticoagulant therapy. The animals were sacrificed at various intervals and the heart was examined grossly and microscopically. Fourteen animals received Dicumarol only, three

received heparin for several hours postoperatively until the effect of Dicumarol was apparent, and 15 did not receive anticoagulants but served as controls.

The incidence and magnitude of hemorrhagic extravasations on the endocardium and pericardium and of miliary hemorrhages in the myocardium were similar in the treated and control animals. In the few dogs with excessively prolonged prothrombin time there was no increase in myocardial hemorrhages. The size of the infarcts and the rate and character of healing did not differ between the treated and control groups. No mural thrombi were found in either group of dogs. The development of collateral anastomoses between the coronary arteries was the same in both groups.

The investigators concluded that Dicumarol produces no adverse effect on the myocardium of dogs which might retard the healing or the development of collateral circulation in experimentally produced myocardial infarction.

Beattie and co-workers³ determined the effect of Dicumarol upon experimental occlusion of the descending branch of the left coronary artery in dogs. Comparison of the control and treated groups showed similar electrocardiographic and pathological findings. Grossly and microscopically, there was no evidence of propagation of coronary thrombi or of formation of mural thrombi in either group. In appearance and size, myocardial infarcts were the same in one group as in the other. Hemorrhage into the infarcted areas was not prominent in either group. Electrocardiographic changes included, singly or in combination, RS-T segment displacements, changes in the direction of the T waves, ectopic rhythms and conduction disturbances typical of those in similar ligation experiments previously reported. Similar changes occurred in the treated and in the untreated animals.

LeRoy and Nalefski¹⁴ investigated the influence of Dicumarol on the healing of experimental myocardial infarction produced by ligation of the descending branch of the left coronary artery in 32 dogs. Dicumarol was administered to 15 dogs, ten dogs served as controls, and seven died within 24 hours. The animals were sacrificed in from five to 21 days postoperatively.

Grossly there was no significant difference in the appearance of the infarcts at any stage of healing. Mural thrombi were not found in any heart. Microscopically, there was no obvious difference between the healing infarcts in the treated dogs and those in the controls. Serial electrocardiographic studies revealed no variation in the rate or character of the evolutionary changes. It was concluded that Dicumarol therapy does not have any demonstrable deleterious influence on the healing of experimental myocardial infarction in dogs.

LONG-TERM THERAPY WITH DICUMAROL

The administration of Dicumarol over long periods of time may be advisable as a prophylaxis against thromboembolism in patients who are pre-

disposed to the repeated occurrence of thromboembolic phenomena. Anticoagulant therapy may be indicated for the remainder of the patient's life. The patient for whom this type of therapy is most definitely indicated is one with rheumatic heart disease complicated by valvular damage and auricular fibrillation with periodic release of showers of emboli to the pulmonary or peripheral circulation. Any patient with heart disease associated with auricular fibrillation or with an intracardiac source of emboli may be a candidate for prolonged anticoagulant therapy.

Wright^{36, 37} reported briefly on a series of patients with rheumatic heart disease and auricular fibrillation who had experienced multiple emboli and to whom Dicumarol was given to prevent the further development of mural thrombi and the subsequent detachment of emboli.

Foley and Wright⁸ reported in considerable detail on these and additional cases. A total of 19 patients had been on Dicumarol for periods of from five to 20 months (average 11 months). The favorable results were no less than dramatic and, in certain instances, patients who had been invalids and in constant fear of death prior to anticoagulant therapy, led completely normal, active lives thereafter.

Sprague and Jacobsen³¹ reported a case in which a patient who had rheumatic heart disease with periodic arterial embolism remained free of thromboembolic complications during 11 months while under ambulatory treatment with Dicumarol.

It may also be advisable to administer anticoagulants over an indefinite period of time to patients with recurrent coronary thrombosis and myocardial infarction. In 1945, Wright³⁵ suggested that the question of continued use of Dicumarol as a prophylactic measure in patients who had experienced a coronary thrombosis warranted further study.

Foley and Wright⁸ reported upon five patients who had coronary thrombosis with myocardial infarction and who were treated with Dicumarol for periods up to nine months. No thromboembolic or hemorrhagic phenomena occurred in these patients during the period of observation, and the patients led essentially normal, productive lives.

Nichol²⁰ and Nichol and Fassett²¹ administered Dicumarol to patients with coronary artery disease over long periods of time. The report by Nichol and Fassett concerned five patients who had had multiple attacks of coronary thrombosis prior to the administration of Dicumarol for periods of from six to 32 months. One patient who was given Dicumarol for 21 months died of acute coronary occlusion which the authors attributed to lack of necessary control of anticoagulant therapy. A second patient had not had an attack for three years while Dicumarol was given, although he had had three attacks of acute coronary occlusion during the 13 months prior to the administration of the anticoagulant. The other three patients had been on Dicumarol for from six to seven months without recurrence of occlusion.

Nichol and Fassett noted a decrease in the amount of angina during the time these patients were taking Dicumarol. They expressed belief that long-term therapy with Dicumarol is rational and safe, providing the prothrombin time is determined carefully and at frequent intervals. Nichol stated that he had administered Dicumarol to 64 patients in 70 attacks of acute coronary thrombosis; 11 died, a mortality rate of 15.7 per cent. In 40 initial attacks so treated, there had been but one death.

Nichol and Borg²² reported further experience with long-term therapy in 68 patients who had had one or more attacks of coronary thrombosis and/or myocardial infarction. At the time of report, 36 patients had been on Dicumarol for three to 12 months, 20 for one to two years, 11 for two to three years, and one for five years. Prothrombin time was determined at weekly intervals after the patient had become ambulatory and an attempt was made to maintain the prothrombin time at a value twice normal, the equivalent of a reduction in the prothrombin activity to between 10 and 30 per cent of normal. The dose of Dicumarol averaged 60 to 75 mg. a day. Hemorrhage occurred in one-fourth of the patients, usually due to the presence of some pathological lesion, or to an overdose of Dicumarol. In only three cases was anticoagulant therapy abandoned because of hemorrhage.

Nine patients discontinued therapy; two of them died later of recurrent attacks of coronary occlusion. Ten patients died while taking Dicumarol, and in six of those cases autopsy was done. There was a fresh coronary thrombosis, or an infarction, in two instances and a cerebral hemorrhage in one instance; in three cases death was ascribed to ventricular fibrillation or to congestive heart failure. In two of the four cases in which autopsy was not done, the patients died of recurrent coronary thrombosis. Of the 49 patients remaining on Dicumarol, all were active in business or household duties. Although four had had episodes of acute coronary insufficiency, infarction had not occurred, and uncomplicated recovery had followed. The patient who had been on Dicumarol for five years without an attack of coronary thrombosis during this time had had three attacks prior to anticoagulant therapy.

THE USE OF DICUMAROL IN CONGESTIVE HEART FAILURE

Patients with congestive heart failure are prone to develop thromboembolic complications which increase the morbidity and mortality of the disease. Kinsey and White¹² reported the presence of pulmonary infarction in 24 of 50 cases of congestive heart failure in which autopsy was done. Carlotti and associates,⁶ in a study of pulmonary embolism in 273 patients admitted to the medical service of a hospital, found that the admission diagnosis in 104 instances was congestive heart failure.

Patients with liver damage are liable to have reduced plasma prothrombin activity and to react in an extremely sensitive manner to a given dose of

Dicumarol (that is, they are liable to be "hyperreactors"). Reisner, Norman, Field and Brown²⁸ determined the prothrombin time in 100 male subjects before and following a single dose of 100 mg. of Dicumarol. No patient was selected whose prothrombin activity was not normal initially. The prothrombin time was determined on whole plasma each day until it had returned to normal. Extensive liver function tests were carried out and observations were made of the size of the liver, the presence or absence of ascites, and the presence and degree of congestive heart failure.

Depression of prothrombin activity to less than 60 per cent of normal occurred in 28 patients, 93 per cent of whom had evidence of liver disease or congestive heart failure. The patients with the most profound depression had extensive liver damage as indicated by the presence of ascites, hepatomegaly, positive reaction to cephalin flocculation tests and inverted albumin-globulin ratios. Among 33 patients with congestive heart failure, 14 (42.4 per cent) were "hyperreactors" as manifested by a depression of prothrombin activity to below 60 per cent following the single test dose of Dicumarol. Three of these patients had other liver disease as well. Twenty other patients with congestive heart failure (57.6 per cent), three of whom had other liver disease as well, did not have a reduction of prothrombin activity to less than 60 per cent of normal following the test dose of Dicumarol.

The high incidence of congestive failure among the hyperreactors to Dicumarol is evidence that hepatomegaly due to congestive failure indicates a physiologically deranged liver. This conclusion is supported by the results of liver function tests. It is also evident that the presence of congestive failure may alter the response to Dicumarol. The response to a single test dose of Dicumarol is a sensitive test of liver function.

Anderson and Hull² administered Dicumarol to alternate patients with congestive heart failure in addition to employing the usual conservative methods of therapy. Patients with plasma prothrombin activity of 50 per cent of normal or less at the time of admission ("low prothrombin group") were not given Dicumarol. The series consisted of 142 patients, consecutive and unselected except for a small number eliminated because of the presence of jaundice, severe angina, or azotemia. Sixty-one were given Dicumarol, 58 served as controls and 23 were in the "low prothrombin group."

There was no correlation between the degree of hepatic enlargement and the reduction of plasma prothrombin activity. However, in 43 per cent of the patients with an initially low prothrombin activity, congestive failure had been first observed more than a year previously, suggesting that the disturbance of prothrombin formation might be related to long-standing or recurrent hepatic congestion.

A reduction of prothrombin activity to 10 to 30 per cent of normal was attained in 52 (85 per cent) of the 61 patients given Dicumarol. Adequate reduction was usually attained within 48 to 72 hours, but

there was pronounced variation in response to Dicumarol in individual cases. Menadione® was given on six occasions when the prothrombin activity fell to below 10 per cent of normal and in each instance the prothrombin level returned promptly toward normal. Hematuria was noted microscopically in several instances, and gross hematuria once in the presence of an indwelling catheter. No serious toxic effects attributable to Dicumarol were observed.

The average duration of hospitalization was almost exactly the same in the three groups. The mortality rate in the treated group was 11 per cent, in the control group 18 per cent, and in the "low prothrombin" group 9 per cent.

Thromboembolism may have been a factor in the death of two patients in the treated group and of seven patients in the control group. One of the two deaths in the "low prothrombin" group may have been related to pulmonary embolism. Definite pulmonary embolism or acute pulmonary infarction occurred in five patients—three in the treated group (but before the first dose of Dicumarol was given) and two in the control group. All five patients recovered. If the proved, probable, and possible instances of thromboembolism, fatal and non-fatal, are pooled, the number of thromboembolic complications in the entire series of 142 cases is 14 (10 per cent). Five (8 per cent) occurred in the treated group and nine (15 per cent) in the control group.

Anderson and Hull summarized: Among 61 patients with congestive heart failure to whom Dicumarol was given, it was possible to reduce and maintain the prothrombin activity at 30 per cent of normal or less in 52 patients (85 per cent) without apparent harm. Among the 61 cases only two suggestive and no certain thromboembolic complications occurred following the administration of Dicumarol. In four patients who had had pulmonary infarction prior to the use of Dicumarol, no further episodes occurred after Dicumarol was given. The mortality rate was lower and the apparent incidence of thromboembolism less in the group of patients who received Dicumarol than was the case in a closely similar group of the same size in which no anticoagulant was employed; but there is no certainty that the difference in mortality rate is significant, or that the apparent difference in the incidence of thromboembolic complications is real.

All patients admitted to the Veterans Administration Hospital in Minneapolis because of cardiac decompensation were treated with Dicumarol after October 1946. The report by Wishart and Chapman³³ is a preliminary evaluation of the therapy as carried out in August 1947. Sixty-one patients with congestive failure were treated with Dicumarol. In 19 patients (31 per cent) auricular fibrillation was present and there were definite signs of mitral stenosis in 11 (18 per cent).

The prothrombin time was determined each day and the prothrombin concentration was kept between 10 and 30 per cent of normal. The average initial prothrombin concentration, before Dicumarol was started, was 62 per cent of normal and in

one case it was only 17 per cent—evidence of seriously impaired liver function secondary to congestive failure. Dicumarol was administered in most cases until the patient was ambulatory or until death supervened. The average daily dose of Dicumarol for an adequate effect was 78 mg., confirming the view that patients in cardiac failure require smaller doses of Dicumarol than do compensated persons. No hemorrhagic complications developed, although it was often necessary to suspend Dicumarol therapy because of excessive depression of the prothrombin activity. Vitamin K was occasionally administered to counteract an excessive Dicumarol effect.

The mortality rate was 32.8 per cent (20 deaths) and 12 autopsies were done. There were no deaths definitely attributable to pulmonary embolism, and in 19 instances death was not suggestive of this complication. Emboli were not found in any of the 12 autopsies. Because of the difficulty of establishing the diagnosis of pulmonary embolism and infarction in every instance, symptoms and signs thereof were carefully sought and thoroughly investigated. Definite pulmonary infarcts developed clinically in two patients on Dicumarol therapy, but during a time when the Dicumarol effect was inadequate. Pulmonary and systemic infarcts were present in six of the 12 cases in which autopsy was done, but in five instances these lesions had developed before or after Dicumarol therapy. In one case pulmonary infarct developed despite adequate doses of Dicumarol.

With the clinical and postmortem evidence combined, it is probable that embolic phenomena developed in four cases (6.5 per cent) despite adequate Dicumarol therapy. Previously published reports indicate that in a group of comparable patients not given anticoagulants, the expectancy would be for pulmonary emboli in more than 20 per cent.

COMMENT

It is apparent that, with the exception of the American Heart Association study, there is no series of patients with heart disease who have been treated with anticoagulants which is of sufficient magnitude, or sufficiently well controlled, to warrant statistical evaluation. However, it ought not be ignored that in every series reported in the literature the results of treatment with anticoagulants have been favorable, consisting usually of a considerable reduction in the incidence of thromboembolic complications and of a more modest, although frequently significant, reduction in the immediate mortality, either in comparison with a control series, or with the anticipated occurrence of such complications and deaths as judged by the literature or the personal experience of the authors.

Nichol²³ observed recently that the composite mortality rate in 656* cases of acute coronary occlusion with myocardial infarction treated with anti-

*The aggregate of cases covered in eight independent reports in the literature (excluding the American Heart Association report and reports of series included in that study).

coagulants was 13.1 per cent. In contrast, he found that the immediate mortality rate for an aggregate of 2,325 cases[†] in which anticoagulant therapy was not used, was 28.8 per cent.

The use of the anticoagulants in the treatment of certain types of heart disease is based upon the frequent occurrence of thromboembolic complications and upon the importance of these complications in increasing the morbidity and mortality rate. The advocates of anticoagulant therapy cite the studies of Eppinger and Kennedy,⁷ Nay and Barnes,¹⁷ Wartman and Hellerstein,³² Hellerstein and Martin,⁹ and Mintz and Katz¹⁶ as evidence that thromboembolic phenomena do complicate certain types of heart disease commonly and that they do significantly increase the immediate morbidity and mortality rates. To those critics who deny the importance of thromboembolism in the types of heart disease mentioned in this review, the answer is, obviously, that they must be overlooking such complications.

The essential problem at present is to attain means whereby the anticoagulants may be administered both effectively and safely to patients with heart disease. As has been acknowledged repeatedly, heparin and Dicumarol can be administered effectively and safely only in experienced hands and where suitable laboratory facilities exist. That hemorrhages do (infrequently) occur as a result of anticoagulants, and that they are often serious and occasionally fatal, is undeniable; but reports of such untoward reactions demonstrate beyond reasonable doubt that the greatest single factor in the production of hemorrhage in the circumstances is human error—erroneous diagnoses, careless or misguided administration, and failure to observe the meticulous management which is essential to the safe and effective use of these drugs.

There is no promise of simpler, more error-proof and more economical laboratory tests for following the course of patients being given anticoagulants. There is no immediate promise of a clinically useful and economical substitute for heparin, although Paritol® or some similar substitute may, in time, prove to be valuable. There is evidence, however, that the coumarin Tromexan®—the ethyl ester of di-(4-hydroxycoumarinyl) acetic acid—may prove to have certain distinct advantages over Dicumarol in clinical practice.

As a practical matter, it must be suggested that the physician who cannot administer the anticoagulants in an expert manner, who cannot obtain exacting laboratory control, and who cannot maintain close observation of patients, should avoid the use of anticoagulants except when the indications are absolute. He should probably use no other anticoagulant than heparin in those instances in which he does administer this type of therapy. He should not attempt to manage patients on long-term therapy but should refer them for that kind of preventive care.

[†]Aggregate of 14 series reported in the literature since 1940.

In circumstances in which laboratory control is precise and the physician can provide meticulous observation of the patient, the anticoagulants may be administered effectively and with a minimum of hazard from hemorrhage if the following essentials are observed in all instances: (1) accurate diagnosis; (2) determination of the clotting time or of the prothrombin time, according to the drug being used, before any anticoagulant is administered and each day thereafter until the response of the patient is clearly determined, whereupon such studies can be made on alternate days, twice a week, or, occasionally, at weekly intervals; (3) exacting laboratory control according to the rigid standards described by all workers in this field of therapy; (4) administration of the anticoagulant to produce the optimum therapeutic effect; (5) frequent and careful observation of the patient; (6) continued administration of the drug until the hazard of thromboembolism is removed. Anything short of these criteria will lead unnecessarily to failure and to the eventual disrepute of therapy of this type.

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